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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,434	09/14/2006	Kirby Siemering, Victoria	18896	6151

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,434	SIEMERING, VICTORIA ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 20-27* is/are pending in the application.

4a) Of the above claim(s) *21-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,20,26 and 27* is/are rejected.

7)☒ Claim(s) *1-17 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/08, 9/13/07*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Claims 1-17, 20, and 26-27 drawn to the specific combination of connexin 26, pendrin, mitochondrial 12s rRNA and usherin and SEQ ID NO. 1 in the reply filed on 4/14/2009 is acknowledged. The traversal is on the ground(s) that although the examiner notes that Hone et al. teach a genotyping method to detect deafness mutations of connexin, that unity of invention has not been argued (p. 3 last two paragraph). The reply asserts that the cited reference does not teach a genotyping method based on the combination of elected genes (p. 3 last paragraph). The reply asserts that the technical features is those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art (p. 4 1st paragraph). The reply asserts that single inventive concept is a genotyping method of a relevant pathological condition is achieved by employing at least one allele specific oligonucleotide (p. 4 1st paragraph). This is not found persuasive because as acknowledged by the reply the technical feature is a genotyping method of a relevant pathological condition is achieved by employing at least one allele specific oligonucleotide. Therefore as stated in the requirement for restriction, as this technical feature is taught by Horne et al., the technical feature fails to make a contribution over the prior art and as such there is no special technical feature between Groups I-VI.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-17 and 20-27 are pending. Claims 18-19 have been cancelled.

3. Claims 21-25 are withdrawn from consideration as drawn to a nonelected invention.

4. An action on the merits for Claims 1-17, 20, and 26-27 is set forth below. As noted in the reply to restriction, applicant has elected the specific combination of connexin 26, pendrin, mitochondrial 12s rRNA and usherin (p. 2) and the specific SEQ ID NO. 1 from SEQ ID Nos 1-64. As such all claims will be examined to the combination of connexin 26, pendrin, mitochondrial 12s rRNA and usherin.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 1/14/2008 and 9/13/2007 have been considered by the examiner.

Claim Objections

6. Claims 1-17 and 20 are objected to because of the following informalities: Claims 1-17 and 20 are objected to because they specifically recite nonelected subject matter. As stated above, applicant has elected the combination of connexin 26, pendrin, mitochondrial 12s rRNA and usherin and the specific SEQ ID NO. 1. Applicant should amend the claims so that the claims are directed to the elected invention. Prior to allowance of these claims, the non-elected subject matter will be required to be, deleted from the claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Appropriate correction is required.

Further Claim 1 contains typographical errors. Mitochondrial 125 should be spelled “mitochondrial 12s” and ussherin should be spelled “usherin”. Claims 1, 16, 17, 20, and 26 contain the typographical error that connexin 26 is spelled “connexion 26”. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-15, 17 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15, 17 and 20 are indefinite over the phrase “2-8X SSC/0.05%” in the 4th step of the hybridization conditions in claims 1, 17, and 20. Because the claim has not defined the chemical which is 0.05% the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-12, 17 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kudo et al. (American Journal of Medical Genetics VOl. 90 p. 141) in view of Smith et al. (Seminars in Pediatric Neurology 2001 VOl 8 p. 147), Sato et al. (European Journal of Endocrinology 2001 VOl. 145 p. 697), Fischel-Ghodsian et al. (US Patent 5506101 April 9, 1996), Najera et al. (Human mutation June 2002 Vol. 20 p. 76 it is noted that for citation purposes the reference is numbers from p. 1-7), and Van Ness (US Patent 5994065 November 30, 1999).

With regard to Claims 1, 17, and 26, Kudo et al teaches the genotyping of the connexin 26 gene for deafness by ASO hybridization (abstract). Kudo et al. teaches genomic DNA was examined by PCR and sequences using the ASO technique (p. 142 1st column last paragraph). Kudo et al. teaches that an allele specific probe on a membrane (e.g. a solid support) was contacted with DNA from connexion 26 (p. 143 1st column last paragraph). Kudo et al. teaches that the DNA was labeled with fluoreciein (e.g. a reporter label) to give a signal (p. 143 1st column last paragraph). Kudo et al. teaches hybridization such that the presence of absence of the reporter molecule can

be screened to determine the genotype of the patient (p. 143 and Table II). Kudo et al. does not teach the specific hybridization constraints.

With regard to claims 2-3, Kudo et al. teaches the DNA is labeled by PCR incorporation and hybridization of the labeled oligonucleotide to the test DNA (p. 143 1st column 2nd paragraph).

With regard to Claims 4-5, Kudo et al. teaches that the subject is human (p 142 1st paragraphs).

With regard to Claims 6-8, Kudo et al. teaches the pathological condition was deafness (p. 142 1st paragraph).

With regard to claim 9, Kudo et al. teaches that the level of the signal is detected and that the nucleotides can have at least one mismatch (figure 1).

With regard to Claims 10-12, Kudo et al. teaches that the probes were immobilized on a membrane and were 17 nucleotides (p. 143 1st column last paragraph and Table 1).

However, Kudo et al. does not teach the specific hybridization constraints nor the genotyping of pendrin, mitochondrial 12s rRNA and usherin.

With regard to Claims 1, 17, and 26, Smith et al. teaches that there are genes that are associated with sensorineural hearing loss (abstract). Smith et al. teaches that connexin 26 is the most common recessive nonsyndromic mutation of deafness (p. 151 1st column last paragraph). Smith et al. teaches that pendrin syndrome is characterized by a nonsyndromic locus DFNB4 (p. 152 2nd full paragraph). Smith et al. teaches mutations such as A1555G in the 12s RRNA gene is associated with nonsyndromic

hearing loss (p. 156 2nd paragraph). Smith et al. teaches that usherin is a common defect for deafness (p. 149 2nd column 1st paragraph). Therefore Smith et al. teaches connexion 26, pendrin, mitochondrial 12s rRNA and usherin are all associated with hearing loss.

With regard to Claims 1, 17, and 26, Sato et al. teaches the detection of the missense mutation H723R in the pendrin gene is associated with hearing loss (abstract). Sato et al. teaches that PCR and then allele specific amplification was performed to genotype the mutation (p. 699 1st column 2nd paragraph). Sato et al. teaches that allele specific amplification was performed with wild type allele specific primers and a mutant allele specific primer (p. 699 1st column 2nd paragraph).

With regard to Claims 1, 17, and 26, Fischel-Ghodsian et al. teaches a method of detecting 12s rRNA gene mutations associated with deafness (column 2 lines 32-36). Fischel-Ghodsian et al. teaches detection of the A1555G mutations as the 12S rRNA mutations associated with deafness (column 6 lines 50-56). Fischel-Ghodsian et al. teaches that an ASO hybridization technique can be performed to detect the mitochondrial mutations (column 4 lines 20-30).

With regard to Claims 1, 17, and 26, Najera et al. teaches mutations of the usherin gene are associated with hearing loss (abstract). Najera et al. teaches that mutations in the usherin gene can be genotypes by performing a nucleic acid (p. 3 1st paragraph).

With regard to Claims 1, 17, and 26, Van Ness teaches a method for hybridization which reduces the non specific background (abstract). Van Ness teaches

a hybridization method which includes hybridization in the presence of 1X SSC at 42 degrees for 60 minutes (column 18 lines 13). Van Ness teaches the hybridization was followed by 4 washes of 1X SSC/0.1% SDS for 1 minute per wash (Column 18 lines 14-16). Van Ness teaches that a final wash with 2X SSC and 0.1% Tween was used (Column 18 lines 14-17). Therefore Van Ness teaches the hybridization constraints of the instant claims.

Therefore it would be prima facie obvious to modify the method of Kudo et al. to further genotype the pendrin, mitochondrial 12s rRNA, and usherin genes as taught by Smith et al, Sato et al., Fischel Ghodsian et al, and Najera et al. using the hybridization constraints of Van Ness. The ordinary artisan would be motivated to genotype all of these genes because Smith et al. teaches that all of these genes are associated with hearing loss. Therefore the ordinary artisan would be motivated to detect all mutations involved in hearing loss including the mutations of pendrin, mitochondrial 12s rRNA, and usherin as taught by Sato et al, Fischel Ghodsian et al, and Najera et al. using the ASO method of Kudo et al. One of ordinary skill in the art would have been motivated to genotype the known genes of connexion 26, pendrin, mitochondrial 12s rRNA and usherin by applying the conventional methodology of ASO hybridization. The ordinary artisan would be motivated to perform routine optimization of the method of Kudo et al. and use the hybridization constraints of Van Ness in order to reduce hybridization backgrounds with a predictable expectation of successful hybridization due to the functional similarities of the washing conditions of Kudo et al. and Van Ness.

10. Claims 13-15 and 27 are rejected over Kudo et al. (American Journal of Medical Genetics VOl. 90 p. 141),Smith et al. (Seminars in Pediatric Neurology 2001 VOl 8 p. 147), Sato et al. (European Journal of Endocrinology 2001 VOl. 145 p. 697), Fischel-Ghodsian et al. (US Patent 5506101 April 9, 1996), Najera et al. (Human mutation June 2002 Vol. 20 p. 76 it is noted that for citation purposes the reference is numbers from p. 1-7), and Van Ness (US Patent 5994065 November 30, 1999) as applied to claims 1-12, 17, and 26 and further in view of Dobrowolski et al. (2004/0038266 February 26, 2004).

Although the combination of Kudo et al, Smith et al., Sato et al, Fischel-Ghodsian et al, Najera et al. and Van Ness teach a method for genotyping a subject for connexin 26, pendrin, mitochondrial 12s rRNA, and usherin, the combination does not teach a method of genotyping connexin 26 wherein the oligonucleotide comprises SEQ ID No. 1.

With regard to Claims 13 and 27, Dobrowolski et al. teaches a method of screening for hearing loss by detection of connexin 26 mutations. Dobrowolski et al. teaches a method of detecting connexin 26 mutations using the sequence of SEQ ID No. 1 (p. 2 paragraph 19). Dobrowolski et al.'s seq id no. 1 comprises the instantly claimed SEQ ID No. 1 (see alignment below) and therefore the genotyping of the connexin mutation in Dobrowolski et al by the methodology of Kudo et al, Smith et al., Sato et al, Fischel-Ghodsian et al, Najera et al. and Van Ness would produce a oligonucleotide which comprises SEQ ID No. 1.

```
Query Match            100.0%;  Score 28;  DB 46;  Length 28;
  Score over Length      100.0%;
  Best Local Similarity   100.0%;  Pred. No. 0.95;
  Matches   28;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;
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Qy          1 TTTTTTTTTTGATCCTGGGGGGTGTGAA 28
              ||||||||||||||||||||||||||||
Db          1 TTTTTTTTTTGATCCTGGGGGGTGTGAA 28
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With regard to Claims 14-15, Dobrowolski et al. teaches detection using a wild type and a missense probe (Table 1). Dobrowolski et al. teaches that the mismatch is upstream of a series of G residues (see SEQ ID No. 4 and 5 in Table 2).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Kudo et al, Smith et al., Sato et al, Fischel-Ghodsian et al, Najera et al. and Van Ness to detect any number of connexin mutations, including the mutation of Dobrowolski et al. using the oligonucleotide comprising SEQ ID No. 1 with a reasonable expectation of success. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply a known ASO hybridization technique use to detect connexin mutations to further genotype other connexin mutations including those represented by SEQ ID No. 1 with the predictable expectation that the connexion 26 mutation will be genotyped.

11. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kudo et al. (American Journal of Medical Genetics VOl. 90 p. 141) in view of Smith et al. (Seminars in Pediatric Neurology 2001 VOl 8 p. 147), Sato et al. (European Journal of Endocrinology 2001 VOl. 145 p. 697), Fischel-Ghodsian et al. (US Patent 5506101 April 9, 1996), Najera et al. (Human mutation June 2002 Vol. 20 p. 76 it is noted that for citation purposes the reference is numbers from p. 1-7), and Dobrowolski et al. (2004/0038266 February 26, 2004).

With regard to Claims 16, Kudo et al teaches the genotyping of the connexin 26 gene for deafness by ASO hybridization (abstract). Kudo et al. teaches genomic DNA was examined by PCR and sequences using the ASO technique (p. 142 1st column last paragraph). Kudo et al. teaches that an allele specific probe on a membrane (e.g. a solid support) was contacted with DNA from connexion 26 (p. 143 1st column last paragraph). Kudo et al. teaches that the DNA was labeled with fluoreciein (e.g. a reporter label) to give a signal (p. 143 1st column last paragraph). Kudo et al. teaches hybridization such that the presence of absence of the reporter molecule can be screened to determine the genotype of the patient (p. 143 and Table II). Kudo et al. does not teach the specific hybridization constraints.

However, Kudo et al. does not teach genotyping of pendrin, mitochondrial 12s rRNA and usherin or the genotyping of SEQ ID No. 1.

With regard to Claims 16, Smith et al. teaches that there are genes that are associated with sensorineural hearing loss (abstract). Smith et al. teaches that connexin 26 is the most common recessive nonsyndromic mutation of deafness (p. 151 1st column last paragraph). Smith et al. teaches that pendrin syndrome is characterized by a nonsyndromic locus DFNB4 (p. 152 2nd full paragraph). Smith et al. teaches mutations such as A1555G in the 12s RRNA gene is associated with nonsyndromic hearing loss (p. 156 2nd paragraph). Smith et al. teaches that usherin is a common defect for deafness (p. 149 2nd column 1st paragraph). Therefore Smith et al. teaches connexion 26, pendrin, mitochondrial 12s rRNA and usherin are all associated with hearing loss.

With regard to Claims 16, Sato et al. teaches the detection of the missense mutation H723R in the pendrin gene is associated with hearing loss (abstract). Sato et al. teaches that PCR and then allele specific amplification was performed to genotype the mutation (p. 699 1st column 2nd paragraph). Sato et al. teaches that allele specific amplification was performed with wild type allele specific primers and a mutant allele specific primer (p. 699 1st column 2nd paragraph).

With regard to Claim 16, Fischel-Ghodsian et al. teaches a method of detecting 12s rRNA gene mutations associated with deafness (column 2 lines 32-36). Fischel-Ghodsian et al. teaches detection of the A1555G mutations as the 12S rRNA mutations associated with deafness (column 6 lines 50-56). Fischel-Ghodsian et al. teaches that an ASO hybridization technique can be performed to detect the mitochondrial mutations (column 4 lines 20-30).

With regard to Claim 16, Najera et al. teaches mutations of the usherin gene are associated with hearing loss (abstract). Najera et al. teaches that mutations in the usherin gene can be genotypes by performing a nucleic acid (p. 3 1st paragraph).

With regard to Claim 16, Dobrowolski et al. teaches a method of screening for hearing loss by detection of connexin 26 mutations. Dobrowolski et al. teaches a method of detecting connexin 26 mutations using the sequence of SEQ ID No. 1 (p. 2 paragraph 19). Dobrowolski et al.'s seq id no. 1 comprises the instantly claimed SEQ ID No. 1 (see alignment below) and therefore the genotyping of the connexin mutation in Dobrowolski et al by the methodology of Kudo et al, Smith et al., Sato et al, Fischel-

Ghodsian et al, Najera et al. and Van Ness would produce a oligonucleotide which comprises SEQ ID No. 1.

```
Query Match             100.0%;  Score 28;  DB 46;  Length 28;
  Score over Length       100.0%;
  Best Local Similarity   100.0%;  Pred. No. 0.95;
  Matches   28;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 TTTTTTTTTTGATCCTGGGGGGTGTGAA 28
              ||||||||||||||||||||||||||||
Db          1 TTTTTTTTTTGATCCTGGGGGGTGTGAA 28
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Therefore it would be prima facie obvious to modify the method of Kudo et al. to further genotype the pendrin, mitochondrial 12s rRNA, and usherin genes as taught by Smith et al, Sato et al., Fischel Ghodsian et al, and Najera et al. and genotype connexin 26 with an oligonucleotide of SEQ ID No. 1. The ordinary artisan would be motivated to genotype all of these genes because Smith et al. teaches that all of these genes are associated with hearing loss. Therefore the ordinary artisan would be motivated to detect all mutations involved in hearing loss including the mutations of pendrin, mitochondrial 12s rRNA, and usherin as taught by Sato et al, Fischel Ghodsian et al, and Najera et al. using the ASO method of Kudo et al. One of ordinary skill in the art would have been motivated to genotype the known genes of connexion 26, pendrin, mitochondrial 12s rRNA and usherin by applying the conventional methodology of ASO hybridization. The ordinary artisan would also be motivated to genotype any connexin 26 mutations by the ASO hybridization technique of Kudo et al. including genotyping the connexin 26 mutation represented by SEQ ID No. 1. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply a known ASO hybridization technique use to detect connexin mutations to further genotype other

connexin mutations including those represented by SEQ ID No. 1 with the predictable expectation that the connexion 26 mutation will be genotyped.

12. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kudo et al. (American Journal of Medical Genetics VOl. 90 p. 141) in view of Smith et al. (Seminars in Pediatric Neurology 2001 VOl 8 p. 147), Sato et al. (European Journal of Endocrinology 2001 VOl. 145 p. 697), Fischel-Ghodsian et al. (US Patent 5506101 April 9, 1996), Najera et al. (Human mutation June 2002 Vol. 20 p. 76 it is noted that for citation purposes the reference is numbers from p. 1-7), Dobrowolski et al. (2004/0038266 February 26, 2004), and Van Ness (US Patent 5994065 November 30, 1999).

With regard to Claim 20, Kudo et al teaches the genotyping of the connexin 26 gene for deafness by ASO hybridization (abstract). Kudo et al. teaches genomic DNA was examined by PCR and sequences using the ASO technique (p. 142 1st column last paragraph). Kudo et al. teaches that an allele specific probe on a membrane (e.g. a solid support) was contacted with DNA from connexion 26 (p. 143 1st column last paragraph). Kudo et al. teaches that the DNA was labeled with fluoreciein (e.g. a reporter label) to give a signal (p. 143 1st column last paragraph). Kudo et al. teaches hybridization such that the presence of absence of the reporter molecule can be screened to determine the genotype of the patient (p. 143 and Table II). Kudo et al. does not teach the specific hybridization constraints.

Kudo et al. does not specifically teach measuring the GI value. However, Kudo et al. teaches determination of the allele frequencies for the polymorphisms (p. 142 2nd column 3rd paragraph). Kudo et al. provides allele frequencies in Table 3. Therefore Kudo et al. teaches a measurement which is normal mutation over the combination of all alleles (e.g. normal and mutant). As such, the teaching of Kudo teaches the same measurement as the GI claimed in Claim 20.

However, Kudo et al. does not teach genotyping of pendrin, mitochondrial 12s rRNA and usherin or the genotyping of SEQ ID No. 1. Kudo et al. further does not teach the hybridization constraints of Claim 20.

With regard to Claim 20, Smith et al. teaches that there are genes that are associated with sensorineural hearing loss (abstract). Smith et al. teaches that connexin 26 is the most common recessive nonsyndromic mutation of deafness (p. 151 1st column last paragraph). Smith et al. teaches that pendrin syndrome is characterized by a nonsyndromic locus DFNB4 (p. 152 2nd full paragraph). Smith et al. teaches mutations such as A1555G in the 12s RRNA gene is associated with nonsyndromic hearing loss (p. 156 2nd paragraph). Smith et al. teaches that usherin is a common defect for deafness (p. 149 2nd column 1st paragraph). Therefore Smith et al. teaches connexion 26, pendrin, mitochondrial 12s rRNA and usherin are all associated with hearing loss.

With regard to Claim 20, Sato et al. teaches the detection of the missense mutation H723R in the pendrin gene is associated with hearing loss (abstract). Sato et al. teaches that PCR and then allele specific amplification was performed to genotype

the mutation (p. 699 1st column 2nd paragraph). Sato et al. teaches that allele specific amplification was performed with wild type allele specific primers and a mutant allele specific primer (p. 699 1st column 2nd paragraph).

With regard to Claim 20, Fischel-Ghodsian et al. teaches a method of detecting 12s rRNA gene mutations associated with deafness (column 2 lines 32-36). Fischel-Ghodsian et al. teaches detection of the A1555G mutations as the 12S rRNA mutations associated with deafness (column 6 lines 50-56). Fischel-Ghodsian et al. teaches that an ASO hybridization technique can be performed to detect the mitochondrial mutations (column 4 lines 20-30).

With regard to Claim 20, Najera et al. teaches mutations of the usherin gene are associated with hearing loss (abstract). Najera et al. teaches that mutations in the usherin gene can be genotypes by performing a nucleic acid (p. 3 1st paragraph).

With regard to Claim 20, Dobrowolski et al. teaches a method of screening for hearing loss by detection of connexin 26 mutations. Dobrowolski et al. teaches a method of detecting connexin 26 mutations using the sequence of SEQ ID No. 1 (p. 2 paragraph 19). Dobrowolski et al.'s seq id no. 1 comprises the instantly claimed SEQ ID No. 1 (see alignment below) and therefore the genotyping of the connexin mutation in Dobrowolski et al by the methodology of Kudo et al, Smith et al., Sato et al, Fischel-Ghodsian et al, Najera et al. and Van Ness would produce a oligonucleotide which comprises SEQ ID No. 1.

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Query Match             100.0%;  Score 28;  DB 46;  Length 28;
  Score over Length       100.0%;
  Best Local Similarity   100.0%;  Pred. No. 0.95;
  Matches   28;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;
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Qy           1 TTTTTTTTTTGATCCTGGGGGGTGTGAA 28
                 ||||||||||||||||||||||||||||
Db           1 TTTTTTTTTTGATCCTGGGGGGTGTGAA 28
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With regard to Claim 20, Van Ness teaches a method for hybridization which reduces the non specific background (abstract). Van Ness teaches a hybridization method which includes hybridization in the presence of 1X SSC at 42 degrees for 60 minutes (column 18 lines 13). Van Ness teaches the hybridization was followed by 4 washes of 1X SSC/0.1% SDS for 1 minute per wash (Column 18 lines 14-16). Van Ness teaches that a final wash with 2X SSC and 0.1% Tween was used (Column 18 lines 14-17). Therefore Van Ness teaches the hybridization constraints of the instant claims.

Therefore it would be prima facie obvious to modify the method of Kudo et al. to further genotype the pendrin, mitochondrial 12s rRNA, and usherin genes as taught by Smith et al, Sato et al., Fischel Ghodsian et al, and Najera et al. and genotype connexin 26 with an oligonucleotide of SEQ ID No. 1. The ordinary artisan would be motivated to genotype all of these genes because Smith et al. teaches that all of these genes are associated with hearing loss. Therefore the ordinary artisan would be motivated to detect all mutations involved in hearing loss including the mutations of pendrin, mitochondrial 12s rRNA, and usherin as taught by Sato et al, Fischel Ghodsian et al, and Najera et al. using the ASO method of Kudo et al. One of ordinary skill in the art would have been motivated to genotype the known genes of connexion 26, pendrin, mitochondrial 12s rRNA and usherin by applying the conventional methodology of ASO hybridization. The ordinary artisan would also be motivated to genotype any connexin

26 mutations by the ASO hybridization technique of Kudo et al. including genotyping the connexin 26 mutation represented by SEQ ID No. 1. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply a known ASO hybridization technique use to detect connexin mutations to further genotype other connexin mutations including those represented by SEQ ID No. 1 with the predictable expectation that the connexion 26 mutation will be genotyped. The ordinary artisan would be motivated to perform routine optimization of the method of Kudo et al. and use the hybridization constraints of Van Ness in order to reduce hybridization backgrounds with a predictable expectation of successful hybridization due to the functional similarities of the washing conditions of Kudo et al. and Van Ness.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Katherine Salmon/
Examiner, Art Unit 1634

/Sarae Bausch/
Primary Examiner, Art Unit 1634